Intramuscular versus Subcutaneous Injection of Soluble and Lispro Insulin: Comparison of Metabolic Effects in Healthy Subjects

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The aim of this study was to compare the glucodynamic effects of soluble insulin and the rapid acting insulin analogue insulin lispro after subcutaneous (s.c.) and intramuscular (i.m.) injection. Twelve healthy male volunteers (age 26.8 ± 1.7 years, BMI 23.2 ± 2.3 kg m^{-2}; mean ± SD) participated in this single-centre, open-labelled, euglycaemic glucose clamp study on four different days. Soluble insulin or insulin lispro (0.2 U kg^{-1}) were injected s.c. or i.m. into the thigh by syringe. The glucodynamic effects were assessed by registering the glucose infusion rates necessary to maintain blood glucose at 5.0 mmol l^{-1} for the subsequent 420 min. Intramuscular injection of soluble insulin led to an earlier peak of metabolic action when compared to s.c. administered soluble insulin (t_{max} 138 ± 29 vs 179 ± 34 min; $p < 0.05$). The maximal metabolic effect and metabolic activity during the first 2 h after i.m. and s.c. injection of soluble insulin were comparable (GIR_{max} 9.7 ± 2.3 vs 7.8 ± 2.3 mg kg^{-1} min^{-1}; n.s., $AUC_{0–120\,min}$ 0.60 ± 0.18 vs 0.50 ± 0.15 g kg^{-1} 120 min; n.s.). Subcutaneous administration of insulin lispro led to a metabolic effect resembling that induced by i.m. application of soluble insulin (t_{max} 116 ± 26 vs 138 ± 29 min; n.s., GIR_{max} 11.1 ± 2.3 mg vs 9.7 ± mg kg^{-1} min^{-1}; n.s.). However, the overall metabolic response during the first 2 h after injection was higher with s.c. insulin lispro ($AUC_{0–120\,min}$ 0.81 ± 0.26 vs 0.60 ± 0.18 g kg^{-1} 120 min; $p < 0.05$). The glucodynamic activity of i.m. applied insulin lispro was comparable to that of lispro s.c.. Following i.m. injection of soluble insulin, the metabolic activity peaked more rapidly than with s.c. administration. In contrast, the metabolic effect of insulin lispro was similar with either route. The time–action profile of i.m. injected soluble insulin lies between that of s.c. applied soluble insulin and insulin lispro. © 1998 John Wiley & Sons, Ltd.

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Introduction

Injection devices commonly used for the subcutaneous (s.c.) administration of insulin have a needle length of 12–13 mm. The depth of the subcutaneous tissue layer at the arm and thigh injection sites in diabetic patients is often less than this length, especially in lean subjects.[1,2] Depending on the injection technique, patients may therefore often inject insulin unwittingly intramuscularly (i.m.)[1–3]

It has been shown previously that i.m. application of both soluble insulin[1–4] and NPH-insulin[5] leads to a faster insulin absorption in comparison to s.c. administration. Whether this leads to respective differences in the metabolic effect of the applied insulin has been demonstrated for NPH[6] but not for soluble insulin. Although a more rapid onset of action of i.m. injected soluble insulin can be anticipated from clinical experience, a quantitative description would be advantageous. Therefore, the first aim of our study was to describe the time–action profiles following i.m. and s.c. application of soluble insulin.

Rapid acting insulin analogues, such as insulin lispro or insulin aspart, are characterized by a faster onset of action, a more pronounced metabolic effect within the first 2 h after injection and a shorter duration of action compared to soluble insulin.[7,8] The second aim of our study was to investigate whether i.m. injection of soluble insulin leads to a time–action profile that is comparable to that of s.c. applied insulin lispro. The third aim was to study if i.m. injection of insulin lispro resulted in an even more rapid effect than s.c. administration.

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Materials and Methods

Twelve healthy male volunteers (age 26.8 ± 1.7 years, BMI 23.2 ± 2.3 kg m^{-2}, mean ± SD) took part in this single-centre, open-labelled study. All subjects abstained from smoking for at least 3 months and were free from concomitant illness. They were on no medication and none had a personal or family history of diabetes mellitus. Volunteers were instructed to abstain from exercise 24 h prior to study days. The study was approved by the local ethical committee and was carried out according to the regulations of the declaration of Helsinki.

After an overnight fast the volunteers arrived at the test room of our clinic at 7.30 am on four study days for an identical experimental procedure. A 17-gauge catheter was inserted into an antecubital vein of the left arm for sampling of plasma glucose and serum insulin and the line kept patent with a slow infusion of 0.15 mmol l^{-1} saline. A dorsal hand vein of the same arm was cannulated in retrograde direction with an 18-gauge double lumen catheter, which was connected to the glucose sensor of a Biostator (Life Science Instruments, Elkhart, IN, USA). The hand was placed in a wooden box which was warmed by a 100 W light bulb to an air temperature of 55 °C. This technique allowed sampling of arterialized venous blood. A third cannula was inserted into a vein of the contralateral arm to infuse glucose (20 % in water). Into the same vein a low-dose baseline insulin infusion (0.3 U kg^{-1} min^{-1}) was administered throughout the experiment by means of a precision infusion pump (Perfusor Secura FT, B. Braun, Melsungen, Germany). After connection to the Biostator and start of the intravenous insulin infusion, a euglycaemic glucose clamp was established, i.e. arterialized venous blood glucose was kept constant at a target level of 5.0 mmol l^{-1} by means of an automatic closed-loop circuit. On a minute-to-minute basis the glucose requirements according to the actual blood glucose concentrations were calculated by a computer built into the Biostator. A pre-programmed glucose clamp algorithm was used, which directed variation in the infusion rates of a mechanical pump integrated into the Biostator.

After a baseline period of 90 min, subjects received injections of 0.2 U kg^{-1} (14.6 ± 2.4 U) of soluble insulin (Actrapid™ (U100), Novo Nordisk A/S, Bagsvaerd, Denmark) or insulin lispro (Humalog™ (U100), Eli Lilly, IN, USA). On two study days soluble insulin was injected: once i.m. and once s.c.. On the other two study days insulin lispro was administered s.c. or i.m. as well. All s.c. and i.m. injections were applied by the same investigator (K.R.) by means of a U100 1.0 ml syringe with a needle length of 13 mm (Micro-Fine IV+, Becton Dickinson, Heidelberg, Germany) into the right thigh, 7 cm lateral to the midpoint of a line between anterior superior iliac spine and the patella. To ensure s.c. insulin application, the needle was inserted with an angle of 45° into a lifted skinfold. To check for penetration of blood vessels the piston of the syringe was drawn back. If aspiration of blood was not possible the tissue fold was moved carefully from lateral to medial and cranial to caudal. Insulin was injected if these movements could be done easily, assuming that this procedure proved that the needle tip was in subcutaneous tissue.

For i.m. injection the volunteers were asked to tense the muscles of the thigh. The skin in the injection area was stretched flat between two fingers and the needle was inserted perpendicularly to its full length. If aspiration of blood was not possible, it was determined that movements of the syringe and needle in a cranial/caudal and medial/lateral direction were not possible without resistance. This was regarded as proof of i.m. positioning of the needle and insulin was injected. The mean of the subcutaneous tissue depth at the anterolateral thigh was reported to be ≤ 7 mm in healthy male volunteers, therefore with a length of 13 mm the needle tip was assumed to be placed intramuscularly.[1,2,4,9]

After insulin application, glucose infusion rates (GIR) were registered during the subsequent 7 h. For determination of plasma glucose (Glucose Analyser II, Beckman Instruments, Munich, Germany) and serum insulin concentrations blood samples were collected at the following time points: –90, –60, –30, 0, 10, 20, 30, 40, 50, 60, 75, 90, 105, 120, 135, 150, 165, 180, 210, 240, 270, 300, 330, 360, 390, and 420 min. If glucose measurements deviated between the laboratory method and the Biostator the latter was recalibrated immediately. Thus, deviations of glycaemia from the target level were assumed to be minimal and subsequently no correction for deviation from the target level was done. Serum insulin was measured as immunoreactive insulin by radioimmunoassay (Pharmacia Insulin-RIA, Pharmacia, Uppsala, Sweden; intra-assay coefficient of variation (CV) 5.8 % at 70 pmol l^{-1} and 5.7 % at 390 pmol l^{-1}, inter-assay CV 9.5 % and 8.3 %).

Statistical Analysis

Results are given as mean ± SD throughout the text and as mean ± SE in Figure 1. Blood glucose concentrations and glucose infusion rates were transferred every minute from the Biostator to an external computer.[10] After the experiments, GIR data were divided by body weight and after subtraction of the basal GIR these minute-to-minute values were used for fitting of a log-normal function.[11] This function was fitted to each individual GIR profile, allowing estimation of the following pharmacodynamic summary measures: maximal GIR (GIR_{max}), time to GIR_{max} (t_{max}), and time to early half-maximal GIR (early $t_{50\%}$). Pharmacokinetic summary measures were evaluated by fitting a polynomial function to each insulin concentration profile: incremental maximal serum insulin concentration (C_{max}) and time to C_{max} (t_{max}). Area under the GIR-profiles (AUC) were calculated by means of the trapezoidal rule. Mean values of 5 min intervals were used for the graphical presentation of the data to allow a better discrimination of the different curves.

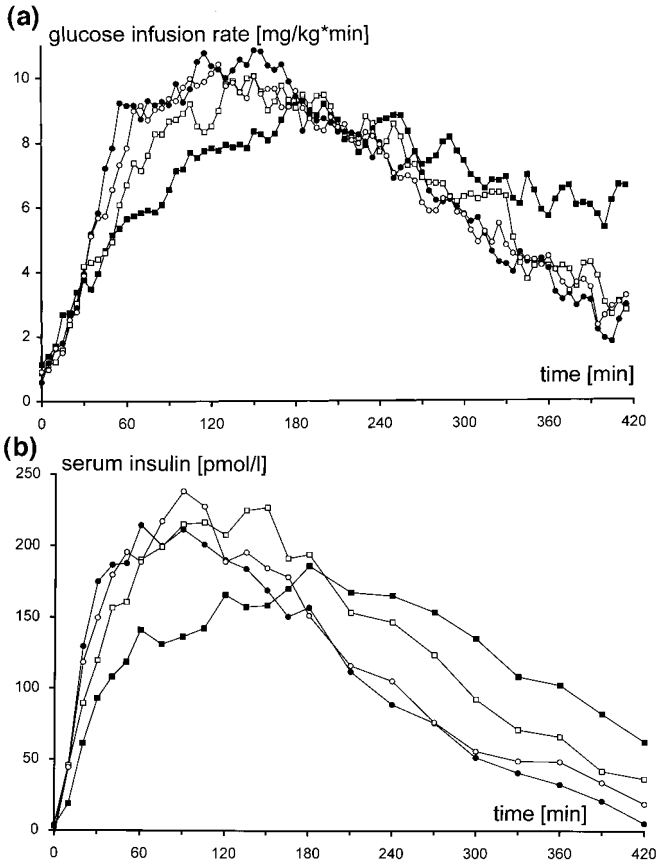

Figure 1. (a) Mean glucose infusion rates and (b) serum insulin concentrations of 12 healthy volunteers after s.c. (■) or i.m. (❐) application (0.2 U kg^{-1}) of soluble insulin and after s.c. (●) or i.m. (○) injection (0.2 U kg^{-1}) of insulin lispro into the thigh

Analysis of variance was used for statistical analysis of the summary measures (randomized-block with multiple Tukey tests). Statistical significance was taken at the 5 % level.

Results

The maximal glucodynamic effect was registered 140 min after i.m. injection of soluble insulin, but 180 min after s.c. administration (Table 1, Figure 1). The maximal metabolic effect (GIR_{max}) achieved by both application techniques was comparable. No differences were observed between the two injection techniques in the metabolic activity during the first 2 h after injection ($AUC_{0–120\ min}$) or overall metabolic effect ($AUC_{0–420\ min}$).

After s.c. injection of insulin lispro the time to maximal metabolic activity was not significantly shorter than with i.m. soluble insulin (Table 1, Figure 1) and the peak metabolic responses were comparable. However, during the first 2 h after insulin administration, the glucodynamic activity of s.c. insulin lispro was higher than after i.m. soluble insulin. The overall glucodynamic effects were similar.

As expected, s.c. injection of insulin lispro led to an earlier peak of action, a higher maximal metabolic activity and a higher metabolic effect during the first 2 h in comparison to s.c. soluble insulin. No glucodynamic differences between insulin lispro following either s.c. or i.m. administration were observed.

Maximal serum insulin concentrations following i.m. administration of soluble insulin were higher (240 vs 180 pmol l^{-1}, Table 1, Figure 1) and were reached 30 min earlier compared to s.c. application (130 vs 160 min) Peak serum insulin concentrations after s.c. injection of insulin lispro were observed 50 min earlier than with i.m. soluble insulin (80 vs 130 min). Insulin $AUC_{0–120}$ of i.m. soluble insulin, s.c., and i.m. insulin lispro were higher than after s.c. soluble insulin. Subcutaneous and i.m. injections of insulin lispro led to similar serum insulin profiles.

Discussion

This study showed that i.m. injection of soluble insulin into the thigh leads to an earlier maximal metabolic effect than s.c. administration. Subcutaneous injection of the rapid-acting insulin analogue insulin lispro resulted in a similar maximal and metabolic effect as i.m. soluble insulin but resulted in a greater glucose consumption during the first 2 h after injection, showing an overall increase in metabolic activity with s.c. insulin lispro. In contrast to soluble insulin, there were no significant glucodynamic differences between s.c. or i.m. administration of insulin lispro.

Faster onset of metabolic response after i.m. injection of soluble insulin compared to s.c. application is well known to the clinician, but, to our knowledge, the quantitative differences between i.m. or s.c. administration have not been documented before. Our study demonstrated that the peak metabolic activity of soluble insulin when applied into the thigh was reached 40 min earlier with i.m. than s.c. injection. This is in accordance with results of insulin absorption studies showing that i.m. injection of soluble insulin resulted in higher absorption rates and/or maximal serum insulin concentrations earlier than with s.c. administration.[2,4,12] Intramuscular administration of soluble insulin might be advantageous in a clinical setting if a more rapid decline in glycaemia is desired, e.g. if a high preprandial glycaemia is measured or for correction of incidental hyperglycaemia. Intramuscular injections of soluble insulin might be an alternative to the use of rapid-acting insulin analogues in pregnant diabetic women, for example. Probably the duration of action of soluble insulin is shorter with i.m. administration compared to s.c. injection, although our protocol was too short to confirm this.

The more rapid absorption of i.m. soluble insulin is said to be due to the higher blood flow in muscle compared to subcutaneous tissue. Physical activity increases the absorption rate of soluble insulin injected into a working muscle compared to resting musculature about twofold.[4,9] However, absorption of soluble insulin

Table 1. Pharmacodynamic and pharmacokinetic summary measures after four different experiments with 12 healthy volunteers. Soluble insulin and insulin lispro (0.2 U kg^{-1}) were administered subcutaneously (s.c.) and intramuscularly (i.m.) on four different occasions

	Soluble insulin s.c.	Soluble insulin i.m.	Insulin lispro s.c.	Insulin lispro i.m.
Glucose infusion rates: pharmacodynamic summary measures				
GIR_{max} (mg kg^{-1} min^{-1})	7.8 ± 2.3[b,d]	9.7 ± 2.3	11.1 ± 2.3	10.4 ± 2.7
Early $t_{50\%}$ (min)	50 ± 14	56 ± 13 [c,e]	44 ± 15	43 ± 10
t_{max} (min)	179 ± 34[a,b,d]	138 ± 29	116 ± 26	120 ± 28
$AUC_{0-120\ min}$ (g kg^{-1} 120 min)	0.50 ± 0.15[b,d]	0.60 ± 0.18[c,e]	0.81 ± 0.26	0.78 ± 0.25
$AUC_{0-420\ min}$ (k kg^{-1} 420 min)	2.55 ± 0.70	2.54 ± 0.74	2.81 ± 0.70	2.78 ± 0.89
Serum insulin levels: pharmacokinetic summary measures				
Basal insulinaemia (pmol l^{-1})	105 ± 18	94 ± 12	102 ± 24	109 ± 19
t_{max} (min)	156 ± 52[a,b,d]	127 ± 47[c]	78 ± 24	91 ± 29
C_{max} (pmol l^{-1})	182 ± 51[a,b,d]	244 ± 52	229 ± 65	236 ± 42
$AUC_{0-120\ min}$ (nmol l^{-1} 120 min)	13.2 ± 3.4[a,b,d]	19.1 ± 6.0	20.6 ± 5.4	20.9 ± 5.5
$AUC_{0-420\ min}$ (nmol l^{-1} 420 min)	54.3 ± 14.1	57.2 ± 10.0	45.9 ± 13.3	49.0 ± 12.2

[a]Denotes significant differences between s.c. vs i.m. soluble insulin, [b]s.c. soluble insulin vs s.c. insulin lispro, [c]i.m. soluble insulin vs s.c. insulin lispro, [d]s.c. soluble insulin vs i.m. insulin lispro, and [e]i.m. soluble insulin vs i.m. insulin lispro respectively.
Results are given as mean ± SD.

after s.c. injection is delayed primarily due to the self-association of insulin monomers to hexamers in insulin preparations. Subcutaneous administration of rapid acting insulin analogues therefore leads to a faster onset of action and a shorter duration of activity than to s.c. soluble insulin.[7,8]

Interestingly, no acceleration of insulin action was observed between i.m. and s.c. insulin lispro. In fact, the glucodynamic and pharmacokinetic properties of insulin lispro by either route were almost identical. This finding suggests that tissue blood supply is of minor importance for the absorption of rapid acting insulin analogues when compared to soluble insulin. With the latter, higher blood flow might induce a more rapid disintegration of the insulin hexamers, which is not of importance with the insulin analogue lispro.

Due to their pharmacodynamic properties rapid acting insulin analogues allow a better postprandial metabolic control than with s.c. injected soluble insulin.[13–15] However, it remains to be clarified in clinical studies if this is also true with i.m. application of soluble insulin. In principle, the glucodynamic and pharmacokinetic data of our study are specific to the injection site studied. The differences in time-action profiles induced by s.c. injections of soluble insulin into different sites such as the thigh or the abdomen have been investigated only rarely. Recently, ter Braak *et al.*[16] compared the metabolic profiles of soluble insulin and of insulin lispro applied s.c. into three different anatomical regions. In their study, the injection site had an influence on the metabolic activity of soluble insulin, but with insulin lispro the differences were smaller. Differences in insulin absorption rates between injection sites are positively correlated with subcutaneous blood flow,[17,18] so it is reasonable to anticipate a more rapid metabolic activity of soluble insulin when injected into a tissue type or region with a high blood supply compared to a tissue or region with lower blood flow.

In a recent study of diabetic children, 31 % of all injections assessed were applied i.m..[19] The risk of unwittingly applying an i.m. injection depends on the injection technique used and the depths of the subcutaneous tissue layer at the injection site. The risk of unintended i.m. injections with a needle length of 12–13 mm must be greater than with the increasingly used needle lengths of 8 mm. Especially for lean diabetic patients who prefer the arm or the thigh as injection site a strict subcutaneous application may be feasible only with a shorter needle length. Although i.m. injections with thick and blunt needles might have been more painful than s.c. applications with older injection devices, with thin and sharp needles in general use nowadays i.m. injections are less painful, about the same as s.c. The volunteers in our study did not report that i.m. injection was more painful than s.c. application.

The differences in the metabolic response induced by i.m. or s.c. injection of soluble insulin may be one source for the well-known considerable intra-individual variability of insulin action.[20]

In summary, i.m. injection of soluble insulin leads to a faster peak metabolic effect when compared to s.c. application. The glucodynamic activity induced by i.m. application of soluble insulin was midway between that of s.c. administered soluble insulin and insulin lispro. These differences of action according to injection route were not apparent with insulin lispro.

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